International Psychogeriatrics (2004), 16:2, 129–140 © 2004 International Psychogeriatric Association
DOI: 10.1017/S1041610204000092 Printed in the United Kingdom

REVIEW

Is MCI really just early dementia? A systematic review of conversion studies

Maddalena Bruscoli[1] and Simon Lovestone[2]

[1] *Geriatrician, Department of Critical Care Medicine and Surgery, Section of Gerontology and Geriatric Medicine, University of Florence, Florence, Italy*

[2] *Professor of Old Age Psychiatry, Section of Old Age Psychiatry, Institute of Psychiatry, London, U.K.*

ABSTRACT

Objectives: Older people commonly present with memory loss although on assessment are not found to have a full dementia complex. Previous studies have suggested however that people with subjective and objective cognitive loss are at higher risk of dementia. We aimed to determine from the literature the rate of conversion from mild cognitive impairment to dementia.

Methods: Systematic review of MedLine, PsychLit and EmBase.

Results: We identified 19 longitudinal studies published between 1991 and 2001 that addressed conversion of mild cognitive impairment to dementia. Overall the rate of conversion was 10% but with large differences between studies. The single biggest variable accounting for between study heterogeneity was source of subjects, with self-selected clinic attenders having the highest conversion rate. The most important factor accounting for heterogeneity within studies was cognitive testing, with poor performance predicting conversion with a high degree of accuracy.

Conclusions: These data strongly support the notion that subjective and objective evidence of cognitive decline is not normal and predicts conversion to dementia. The more stringent the measures of both variables the better the prediction of conversion. Mild cognitive impairment, appropriately diagnosed, is a good measure with which to select subjects for disease modification studies.

Key words: Mild Cognitive Impairment, aging, Alzheimer's disease

Correspondence should be addressed to: Professor Simon Lovestone, Section of Old Age Psychiatry, De Crespigny Park, London SE5 8AF, U.K. Email: s.lovestone@iop.kcl.ac.uk Tel: +44 20 7848 0550. Fax: +44 20 7848 0632. Received 6 Dec 2002; returned to authors for revision 7 Mar 2003; revised version received 6 Jun 2003; accepted 11 Jun 2003.

Background

Neuropathological and neuroimaging evidence suggests that biological changes associated with dementia, and Alzheimer's disease (AD) in particular, occur long before, perhaps decades before, the onset of symptoms (Bookheimer *et al.*, 2000; Braak and Braak, 1998). Given this, it is therefore probable that there are indicators of incipient dementia occurring before the onset of the full dementia syndrome. The search for such indicators has been extensive, but complicated by the fact that memory complaints in the elderly are common (Jonker *et al.*, 2000).

Over the past 10 years there have been a number of attempts made to define a distinct syndrome of abnormal cognition not amounting to dementia but distinguished from normality. Thus arose such concepts as age-associated memory impairment (AAMI), distinguishing the memory decline of the elderly from normal cognition in young people, and benign senescent forgetfulness (BSF) distinguishing abnormal memory loss in elderly people relative to age-matched controls. However, the syndrome that appears to have become widely accepted is that of mild cognitive impairment (MCI) (Flicker *et al.*, 1991). Although there are a number of different definitions of MCI, the general concept is of subjective memory impairment in the context of cognitive impairment relative to age-matched controls and yet no loss of function and no dementia.

This, now firmly established concept, has huge potential value. Disease modification therapies have been developed for AD and are now undergoing clinical evaluation. It is possible that a disease-modifying therapy will have only limited use in those with established disease because of extensive neuronal loss. Therefore one possible therapeutic approach would be to test new drugs and to use proven disease-modifying compounds in those at risk of developing dementia. If MCI is the harbinger of dementia, then people with this syndrome might be suitable cases for evaluation and treatment. However, equally important is the effect of subjective memory complaints upon the person themselves – what are the prognostic implications of a diagnosis of MCI?

For these reasons, it is essential to know the conversion rate from a diagnosis of MCI to a diagnosis of dementia. Early reviews found a wide range of conversion rates reflecting small studies and variable definitions of the MCI concept (Dawe *et al.*, 1992). Since then there have been a number of advances, including the consolidation of diagnostic categories, and a number of large longitudinal studies have now examined the conversion of MCI to dementia, assessing both the rates over time and factors associated with conversion. We therefore conducted a systematic review and meta-analysis of such studies.

Methods

We first established minimum criteria for inclusion in the review. Studies would be included if they included longitudinal, prospective data with defined criteria for MCI (or equivalent) and defined end-points for conversion. Where we were able to identify such, we specifically did not include studies that used criteria designed to capture cognitive difficulties thought to be normal for age, such as age-associated memory impairment. It remains uncertain whether such memory impairment is truly normal but it is clear that using criteria that define memory impairment relative to young people captures large numbers of the elderly and a different, albeit overlapping, group to those with MCI (Ritchie *et al.*, 2001). We limited papers to those published between 1991 and 2001. We searched the PubMed Medline, PsychLit and EmBase databases using the following terms: Mild Cognitive Impairment, Age-Associated Memory, Late-Life Forgetfulness, Cognitive Decline, mild cognitive* and age + memory. In addition, we hand-searched reference lists of reviews and all included papers. Abstracts were scrutinized and papers retrieved if it was possible that the study met our criteria. The final database interrogation was in January 2002.

In order to avoid duplication of data, only the largest study was included, where a single centre reported multiple studies (examining for example different factors associated with conversion), unless it was made clear that the datasets were not overlapping.

After eligible papers had been identified, a form was generated including all the relevant variables which were then independently extracted from the paper by both authors.

Annual conversion rate of MCI to dementia was calculated by dividing observed conversion rate by time of follow up. For meta-analysis, the mean conversion rate of the whole sample of 1616 subjects was then calculated.

Results

We identified over 3900 papers using the keyword and reference list search. From perusal of the abstracts, over 70 papers were retrieved and of these 19 papers met the study inclusion criteria. The core retrieved data is presented in Table 1 (Bowen *et al.*, 1997; Bozoki *et al.*, 2001; Daly *et al.*, 2000; Devanand *et al.*, 1997; Flicker *et al.*, 1991; Grober *et al.*, 2000; Hogan and Ebly, 2000; Huang *et al.*, 2000; Jack, Jr. *et al.*, 1999; Johansson and Zarit, 1997; Kluger *et al.*, 1999; Li *et al.*, 2001; Morris *et al.*, 2001; Paykel *et al.*, 1998; Petersen *et al.*, 1999; Ritchie *et al.*, 2001; Tierney *et al.*, 1996; Visser *et al.*, 1999; Wolf *et al.*, 2000). There was considerable heterogeneity in the criteria to define MCI, the source

Table 1. Prospective studies of conversion from Mild Cognitive Impairment to dementia

STUDY	CRITERIA	MEAN AGE (Y)	SOURCE	MEAN FOLLOW-UP (MONTHS)	N	CONVERSION TO:	ANNUAL CONVERSION RATE
Bowen *et al.* (1997)	Psychological deficits/ no dementia	73.7	Clinic attenders	48	21	DSM-IIIR dementia	12.0
Bozoki *et al.* (2001)	Psychological deficits/ MMSE >23/not depressed	70.0	Clinic attenders	48	48	AD (clinician diagnosis)	16.6
Devanand *et al.* (1997)	CDR 0 or 0.5/no dementia plus cognitive impairment or questionable dementia	76.4	Clinic attenders	30	75	DSM-IIIR dementia	16.5
Flicker *et al.* (1991)	GDS = 3	71.3	Clinic attenders	25	32	Dementia (clinical assessment)	31.1
Huang *et al.* (2000)	Psychological deficits/ no functional decline/ no dementia	61.2	Clinic attenders	26	31	NINCDS-ADRDA AD	22.5
Petersen *et al.* (1999)	CDR 0.5/not demented	80.9	Clinic attenders	48	76	NINCDS-ADRDA AD	12
Tierney *et al.* (1996)	MMSE > 24/ no functional decline/ no dementia	73.9	Clinic attenders	24	138	NINCDS-ADRDA AD	10.9
Wolf *et al.* (2000)	Psychological deficits/ no dementia	72.0	Clinic attenders	29	27	DSM-IIIR dementia	12.2
Ritchie *et al.* (2001)	Subjective memory complaint, not demented, score > 1SD below mean for age	> 65	Community-living volunteers	24	308	DSM-IIIR dementia	5.6

Table 1. Continued

STUDY	CRITERIA	MEAN AGE (Y)	SOURCE	MEAN FOLLOW-UP (MONTHS)	N	CONVERSION TO:	ANNUAL CONVERSION RATE
Daly *et al.* (2000)	CDR 0.5	72.2	Community-living volunteers	36	123	NINCDS-ADRDA AD	6.3
Grober *et al.* (2000)	Blessed information and concentration score > 8/no dementia	79.4	Community-living volunteers	60	68	DSM-IIIR dementia	6.2
Hogan *et al.* (2000)	ICD-10 type 2 MCI	80.0	Community-living volunteers	60	210	DSM-IIIR dementia	6.8
Jack *et al.* (1999)	CDR 0.5/not demented	77.7	Community-living volunteers	33	80	NINCDS-ADRDA AD	12.4
Johansson *et al.* (1997)	Not demented, mild impairment on cognitive tests	84–90	Community-living volunteers	24	70	DSM-IIIR dementia	18
Kluger *et al.* (1999)	Cognitively normal or mildly impaired (GDS1-3)	70.5	Community-living volunteers	46	179	NINCDS-ADRDA AD	8.2
Li *et al.* (2001)	MMSE 26–24, DSM-IIIR MCI	68.7	Community-living volunteers	44	19	Clinical diagnosis AD	13.5
Morris *et al.* (2001)	CDR 0.5/uncertain dementia	76.4	Community-living volunteers	61	53	CDR >= 1	4.0
Paykel *et al.* (1998)	Minimal dementia	N/s	Community-living volunteers	28	22	CAMDEX dementia	17.8
Visser *et al.* (1999)	Minimal dementia	78.8	Community-living volunteers	13	36	NINCDS-ADRDA AD	23.1

and age of subjects and the length of follow up. In 11 studies, subjects were community-living volunteers, including both those identified through advertisements and those randomly or comprehensively recruited, whereas in the remainder, subjects were selected from specialist services in some context – attenders at clinics, both regular geriatric clinics and specialized memory clinics or from registries of previous attenders at specialist clinics. The follow-up period ranged from a minimum of 1.5 years to a maximum of 10 years and, whilst in some studies follow-up was at fixed points relative to baseline assessment, in others follow-up was for all subjects at a given time-point, leading to considerable within-study heterogeneity in some cases. In most studies the sample size was small and only five examined more than 100 subjects with MCI. Many of the included studies have a larger 'headline' subject number inclusion figure than that cited in Table 1 – we have only examined that portion of the subject group with MCI (as opposed to subjective memory complaints but not MCI or MCI plus signs of dementia).

Annual conversion rates from MCI to dementia vary in these studies from 2% to 31%. A meta-analysis of all 1616 subjects included gave a calculated mean annual conversion rate of 10.24% (95% CI 6.9–11.9), although this figure disguises the considerable heterogeneity of outcomes – ranging from just over 2% to over 30% per year. The mean age of subjects at baseline was 74.1 years (95% CI 71.0–76.7) and at this age, the mean incidence of dementia is 1.82 (95% CI 1.38–2.38) (Petersen *et al.*, 2001; Bachman *et al.*, 1993).

We examined three factors that might explain the heterogeneity in the conversion rate to dementia between studies. Firstly, as the incidence of AD and dementia increases with age, one might expect an increase in conversion from MCI to dementia in older populations not due to the MCI but simply due to age. Similarly as populations age with follow-up, then the conversion rate might increase with length of follow-up, not due to MCI, but simply due to study population aging effects. We therefore correlated age and length of follow-up with conversion rate across studies but found no significant correlation for age (-0.12) or for length of follow-up (-0.58). Finally we hypothesized that subject selection effects might alter the observed conversion rate so we therefore compared conversion rate in those studies utilizing clinic attender populations to those studying community-dwelling volunteers. There was a difference in mean annual conversion with respect to the source of the subjects, in that those studies recruiting from clinic settings reported the highest conversion rates and those from the community the lowest. Overall, the conversion rate for clinic attenders was twice that of the community subjects 15.01 vs. 7.5, $p < 0.05$). Given that even community volunteers are self-selected, then the true rate of conversion for MCI in the community is most likely even lower than the mean reported here. All of the

papers that we examined compared converters with non-converters for variables that might help to discriminate between these categories (Table 2). Not surprisingly, no study examined the same set of variables, rendering comparisons between studies difficult. Six studies, comprising 665 subjects with MCI, showed a greater proportion of conversion in older subjects, and of those that analyzed conversion by gender, two studies with a total of 278 subjects found greater conversion in women, although one study of 53 subjects found no effect of gender. Other factors known to be associated with risk of dementia *per se* include education, which was not a factor affecting conversion rate in the two studies that examined for this, and ApoE status which did affect conversion rate in two studies with a total of 133 subjects, but not in another with 138 subjects. However, the most striking result was that every single study of MCI that we identified showed that baseline neuropsychological performance was impaired in MCI subjects who go on to convert to dementia, relative to those who do not.

Discussion

In the course of this study, Petersen and co-workers (Petersen *et al.*, 2001) reported a systematic review carried out under the auspices of the American Academy of Neurology. The timing of this report was unfortunate as only studies included up to early 2000 were included – a total of 6 separate studies. Since the report of Petersen and colleagues (Petersen *et al.*, 2001), we identified an additional 12 studies comprising 13,500 subjects with MCI. In addition, we extended previous reviews by examining for factors that might contribute to the all-important distinction between those with MCI who go on to progress to dementia and those who remain mildly cognitively impaired.

There is considerable heterogeneity in rates of conversion shown in the studies collected here, with annual conversion rates of 2–31%. The overall conversion rate of 10.2% is five times the expected incidence of dementia of people of this age. We predicted that the age of the cohort and length of follow-up would be important possible confounders increasing conversion rate (as incidence of dementia is not linear but increases with age). However, this did not appear to be the case for age, as both the lowest and the highest conversion rates had mean subject ages within the mid-range for these studies. With respect to follow-up, whilst there was no apparent overall pattern, the highest conversion rate occurred in the study with the shortest follow-up and the lowest conversion rate occurred in the study with the longest follow-up – not what we had predicted. However, apart from these two studies, there was little effect of length of follow-up on annual conversion rates. However, we did find a striking and significant

Table 2. Variables that predict conversion of MCI to dementia

	VARIABLES						
STUDY	AGE	GENDER	APOEϵ4 STATUS	EDUCATION	NEUROPSYCHOLOGICAL TESTS	NEUROIMAGING	EEG
Bowen *et al.* (1997)					Yes		
Huang *et al.* (2000)					Yes		Yes
Flicker *et al.* (1991)					Yes		
Tierney *et al.* (1996)			No		Yes		
Wolf *et al.* (2000)	No				Yes	Yes	
Jack *et al.* (1999)	Yes		Yes (ns)		Yes	Yes	
Hogan *et al.* (2000)	Yes	Yes			Yes		
Grober *et al.* (2000)	Yes	Yes		No	Yes		
Boziki *et al.* (2001)	No				Yes		
Arnaiz *et al.* (2001)					Yes	Yes	
Morris *et al.* (2001)	Yes	No	Yes	No	Yes		
Daly *et al.* (2000)					Yes		
Jelic *et al.* (2000)					Yes		Yes
Devanand *et al.* (1997)	Yes	No		No	Yes		
Kluger *et al.* (1999)	Yes			Yes (predictive power low)	Yes		
Li *et al.* (2001)					Yes (depression)		

difference between studies that recruited from clinic attenders to those that recruited community volunteers. Despite broadly comparable diagnostic criteria, the conversion rate in clinic attenders was twice that of volunteer-based studies. This finding, suggesting that subjects seeking help for memory problems have a high risk of dementia, is in line with previous findings that one of the strongest predictors of conversion, although not sufficient in itself, is subjective memory complaint (Jonker *et al.*, 2000).

Apart from group effects between studies, it is clear, when the individual factors are examined, that one factor above all others predicts conversion from MCI to dementia. In every single one of the studies examined in this review the results of baseline cognitive testing was considerably lower in those who became demented than in those remaining in the MCI category. This was true both for those studies that set out to examine this hypothesis and for others where the primary aim was to examine for some other factor that might predict conversion. Moreover, in many instances the cognitive testing is relatively simple. Thus, for example, Huang and colleagues (Huang *et al.*, 2000) set out to examine whether EEG parameters would predict conversion. Antero-posterior localization of alpha wave activity discriminated between converters and non-converters with 77% accuracy, but it is noteworthy that the mean MMSE of converters was 2 points lower than non-converters, a significant difference. Hogan and Ebly (Hogan and Ebly, 2000) also found the MMSE to be useful in discrimination, giving a specificity of 56% and sensitivity of 79% at prediction when combined with subject age and informant report of memory impairment. Indeed, cognitive testing itself may not even be necessary to predict conversion, as eight simple questions pertaining to judgement and activities directed to an informant, when combined with a CDR rating, correctly predicted, 88.6% of those who went on to convert to dementia (Daly *et al.*, 2000).

These data are consistent and striking. At the very least they demonstrate that a sub-group of those with MCI who are very likely to go on to develop dementia within a few years can be discriminated from those who are less likely to do so using assessments that are part of normal current clinical practice. However, one interpretation of the data would be that MCI is simply early dementia by another name. The papers reviewed here use definitions of MCI that do differ somewhat despite attempts by ICD and DSM to standardize diagnosis in this area. This is highlighted in the study of Hogan and Ebly, (Hogan and Ebly, 2000) who examined a cohort of 892 elderly individuals on two occasions separated by five years. Applying seven different criteria for cognitive impairment not dementia gave prevalence rates of 6% to 29% and conversion rates to dementia of 20% to 50% over the 5 years of the study. The highest conversion rates in fact were from MCI as defined by ICD and DSM. In fact, using DSM-IIIR type 2 MCI as a definition, less than 25% remained alive and free from dementia

after 5 years. MCI as so defined includes memory impairment and personality or some other cognitive change but no functional decline. All of the studies we included in this review also adhered to these criteria. The difference between MCI and dementia is therefore contained in the lack of functional decline. However, the studies we have reviewed include few (and in many cases no) details of how function was assessed and in fact it is far from clear whether there are standardized assessments of function applicable to all people. Identifying relatively subtle functional difficulties in elderly people is difficult and there are significant individual, gender and ethnicity based variation in what counts as function. Thus in Daly and colleagues (Daly *et al.*, 2000), questions about function best discriminated between those with CDR score of 0.5 who went on to become demented and those who did not, although it could be argued that a CDR score of 0.5 combined with reported loss of function would meet the criteria for dementia in the first place.

In summary, these studies show some heterogeneity in conversion rates and not all those with MCI do go on to become demented even in those studies with follow-up to five years or more. It follows that there might be value to be had from developing assessments that discriminate between those who go on to convert to unequivocal dementia from those who do not, even if the suspicion is that MCI really is early dementia by another name in the majority of cases. The remarkably consistent finding that basic cognitive testing and simple functional assessments show very significant baseline differences between converters and non-converters suggests that these routine assessments will prove more useful in prediction of conversion than the more inconsistent findings, with respect to genetic testing or the more technologically-based approaches.

The concept of MCI may well be useful in trials of prospective disease-modifying therapies where delay in conversion to unequivocal dementia could be a clinically appropriate target. However, we would argue that until more systematic assessments of function are incorporated into the diagnosis of MCI, the concept as currently used in research will continue to include individuals who would be described as having dementia in other, less research-bound, contexts. Equally, applying the concept of MCI to populations not identifying themselves as having memory problems is very likely to select subjects with a low rate of conversion not very much higher than the general population. So we are forced to conclude that good clinical judgement remains essential in diagnosis and that significant concern in the subject and from informants about memory impairment, objective evidence of mild cognitive deficits and reported personality changes most often occur in dementia, and if it walks like a duck and talks like a duck, it probably is a duck whether or not diagnostic manuals recognize it as such.

References

Arnaiz, E., Jelic, V., Almkvist, O., Wahlund, L. O., Winblad, B., Valind, S., *et al.* (2001). Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. *Neuroreport*, 12, 851–855.

Bachman, D. L., Wolf, P. A., Linn, R. T., Knoefel, J. E., Cobb, J. L., Belanger, A. J., *et al.* (1993). Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology*, 43, 515–519.

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., *et al.* (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine*, 343, 450–456.

Bowen, J., Teri, L., Kukull, W., McCormick, W., McCurry, S. M., *et al.* (1997). Progression to dementia in patients with isolated memory loss. *Lancet*, 349, 763–765.

Bozoki, A., Giordani, B., Heidebrink, J. L., Berent, S. and Foster, N. L. (2001). Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Archives of Neurology*, 58, 411–416.

Braak, H. and Braak, E. (1998). Evolution of neuronal changes in the course of Alzheimer's disease. *Journal of Neural Transmission*, 105 *(Suppl)*. 53, 127–140.

Daly, E., Zaitchik, D., Copeland, M., Schmahmann, J., Gunther, J., *et al.* (2000). Predicting conversion to Alzheimer disease using standardized clinical information. *Archives of Neurology*, 57, 675–680.

Dawe, B., Procter, A. and Philpot, M. (1992). Concepts of mild memory impairment in the elderly and their relationship to dementia: a review. *International Journal of Geriatric Psychiatry*, 7, 473–479.

Devanand, D. P., Folz, M., Gorlyn, M., Moeller, J. R. and Stern, Y. (1997). Questionable dementia: clinical course and predictors of outcome. *Journal of the American Geriatrric Society*, 45, 321–328.

Flicker, C., Ferris, S. H. and Reisberg, B. (1991). Mild cognitive impairment in the elderly: predictors of dementia. *Neurology*, 41, 1006–1009.

Grober, E., Lipton, R. B., Hall, C. and Crystal, H. (2000). Memory impairment on free and cued selective reminding predicts dementia. *Neurology*, 54, 827–832.

Hogan, D. B. and Ebly, E. M. (2000). Predicting who will develop dementia in a cohort of Canadian seniors. *Canadian Journal of Neurological Science*, 27, 18–24.

Huang, C., Wahlund, L. O., Dierks, T., Julin, P., Winblad, B., *et al.* (2000). Discrimination of Alzheimer's disease and mild cognitive impairment by equivalent EEG sources: a cross-sectional and longitudinal study. *Clinical Neurophysiology*, 111, 1961–1967.

Jack, C. R., Jr., Petersen, R. C., Xu, Y. C., O'Brien, P. C., Smith, G. E., *et al.* (1999). Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*, 52, 1397–1403.

Jelic, V., *et al.* (2000). Quantitative electroencephalography in mild cognitive impairment: longitudinal changes and possible prediction of Alzheimer's disease. *Neurobiological Aging*, 21, 533–540.

Johansson, B. and Zarit, S. H. (1997). Early cognitive markers of the incidence of dementia and mortality: a longitudinal population-based study of the oldest old. *International Journal of Geriatric Psychiatry*, 12, 53–59.

Jonker, C., Geerlings, M. I. and Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population-based studies. *International Journal of Geriatric Psychiatry*, 15, 983–991.

Kluger, A., Ferris, S. H., Golomb, J., Mittelman, M. S. and Reisberg, B. (1999). Neuropsychological prediction of decline to dementia in nondemented elderly. *Journal of Geriatic Psychiatry and Neurology*, 12, 168–179.

Li, Y. S., Meyer, J. S. and Thornby, J. (2001). Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired elderly. *International Journal of Geriatrric Psychiatry*, 16, 718–727.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., *et al.* (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology*, 58, 397–405.

Paykel, E. S., Huppert, F. A. and Brayne, C. (1998). Incidence of dementia and cognitive decline in over-75s in Cambridge: overview of cohort study. *Social Psychiatry and Psychiatric Epidemiology*, 33, 387–392.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., *et al.* (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology*, 56, 303–308.

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., *et al.* (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 56, 1133–1142.

Ritchie, K., Artero, S. and Touchon, J. (2001). Classification criteria for mild cognitive impairment: A population-based validation study. *Neurology*, 56, 37–42.

Tierney, M. C., Szalai, J. P., Snow, W. G., Fisher, R. H., Nores, A., *et al.* (1996). Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology*, 46, 661–665.

Visser, P. J., Scheltens, P., Verhey, F. R., Schmand, B., Launer, L. J., *et al.* (1999). Medial temporal lobe atrophy and memory dysfunction as predictors for dementia in subjects with mild cognitive impairment. *Journal of Neurology*, 246, 477–485.

Wolf, H., Ecke, G. M., Bettin, S., Dietrich, J. and Gertz, H. J. (2000). Do white matter changes contribute to the subsequent development of dementia in patients with mild cognitive impairment? A longitudinal study. *International Journal of Geriatric Psychiatry*, 15, 803–812.